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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,681	ROTH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,19,53-57 and 75-91* is/are pending in the application.

4a) Of the above claim(s) *7,56,57,77-83 and 86-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,19,53-55,75,76,84 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,6,7,19,53-57 and 75-91* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-07, 9-07, 3-07, 2-07, 1-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2, 6, 7, 19, 53-55, in part, 75, 76, in part, 83, 84, and 85, in part, drawn to a method of identifying a subject at risk of breast cancer by detecting a polymorphism in a region between about chromosome position 87330326 to about 87342924, classified in class 435, subclass 6.

XII. Claims 1, 2, 19, 53-55, in part, 77, 78, 86 and 87 drawn to drawn to a method of identifying a subject at risk of breast cancer by detecting a polymorphism in a region between about chromosome position 87352676 to about 87369072, classified in class 436, subclass 6.

XIII. Claims 1, 2, 19, 53-55, in part, 79, 80, 88 and 89, drawn to drawn to a method of identifying a subject at risk of breast cancer by detecting a polymorphism in a region between about chromosome position 8711012 to about 87314967, classified in class 435, subclass 6.

XIV. Claims 1, 2, 19, 53-55, in part, 82, 83, 90 and 91, drawn to drawn to a method of identifying a subject at risk of breast cancer by detecting a polymorphism in a region between about chromosome position 87320287 to about 87320855, classified in class 435, subclass 6.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, XII-XIV are directed to related methods. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially

different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design and mode of operation. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

3. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

4. Claims 1, 2, 19, 53, 55, in part, directed to the chromosome positions in Group I above, and claims 75 and 84, link(s) inventions in claims 6, 7, 54, 76, 83, and 85. The restriction

requirement among the linked inventions is **subject to** the nonallowance of the linking claim(s), claims. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

5. The newly amended and submitted claims set forth in the restriction requirement above are directed to inventions that is independent or distinct from the invention originally claimed for the reasons set forth above.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1, 2, 19, 53, 55, in part drawn to the chromosome regions set forth in groups XII-XIV above, as well as claims 7, 56-57, 77-83, and 86-91 are withdrawn from

consideration as being directed to non-elected inventions as set forth above and in the previous office actions. See 37 CFR 1.142(b) and MPEP § 821.03. It is noted that claims 7 and 83 are withdrawn as they are drawn to non elected positions, and claims 6, 54, 76, and 85 are examined in so far as they are drawn to the polymorphism at position 87342924 which corresponds to position 36424 of SEQ ID NO: 2, rs154988, the originally elected polymorphic position (see previous office action).

Therefore, an action on the merits of claims 1, 2, 6, 19, 53-55, 75-76, and 84-85, as indicated above, is set forth below. All the amendments and arguments have been thoroughly reviewed but are not sufficient to place the application in condition for allowance. The following rejections constitute the complete being applied to the claims. Response to applicant's arguments follows, where applicable. This action is Non-Final.

Claim Rejections - 35 USC § 112

6. Claims 1-2, 19, 53, 55, 75, and 84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying a human subject at risk of breast cancer comprising detecting the presence or absence of one or more polymorphic variations associated with breast cancer, in a region between about chromosome position 87330326 (position 23826 of SEQ ID NO: 12; rs2575674 and about chromosome position 87342924 (position 36424 of SEQ

ID NO: 2; rs1541998) according to build 33 of Genbank, whereby the presence of the polymorphic variation is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass detection of any polymorphism in over 12kb of the human MAPK10 sequence of SEQ ID NO: 2. However, the specification only the specification only teaches the identification of 9 particular statistically associated polymorphisms out of 16 polymorphic variants found in this region of SEQ ID NO: 2 in humans (see table 19). Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from table 19, that a polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 2 is not predictably associated with breast cancer. The specification teaches no structure/function correlation between the members of the genus of specific polymorphisms in the claimed region that are associated with breast cancer risk. Of 16 polymorphisms taught, only 9 had a p value less than 0.05 (see table 12).

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in over 12kb of the MAPK10 gene. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. The specification only teaches of 9 particular polymorphisms for which data is provided (eg: T/C at position 36424 of SEQ ID NO: 2). With regard to the elected position, the specification teaches that a T at position 36424 of SEQ ID NO: 2 was statistically associated ($p=0.0070$) with breast cancer (table 6B). Thus, applicant has express possession of only 9

particular polymorphisms in SEQ ID NO: 2 which are associated with breast cancer, in a genus which comprises thousands of different possibilities.

The broad variable genus is not represented by the particularly named variants in table 19 of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer or therapeutic response is provided. However, no predictable correlation between the structural alterations of the 9 polymorphisms disclosed and breast cancer is provided by the specification. The specification does not teach the function of polymorphisms of this MAPK10 region nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response. The specification teaches 16 SNPs (table 19) were found in the claimed region of SEQ ID NO: 2, but that only 9 particular polymorphisms exhibited a p value of less than 0.05. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association. It is further noted that the claims (6, 54) broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 36424 of SEQ ID NO: 2), but only teaches 2 out of 4 possible variations at each position (T/C at position 36424). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether the particular nucleotide variant even exists. The specification provides no guidance that any alteration in the claimed region of MAPK10 gene is diagnostic for increased risk for breast cancer.

These claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. The polymorphisms shown are not representative of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within the claimed MAPK10 region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the breast cancer may be tens of thousands of nucleotides distant from the polymorphisms described in the specification.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.)

In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is

required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Response to Arguments

7. The responses dated 5/28/2007 and 8/1/2007 traverse the rejection. The responses as well as the declaration under 37 CFR 1.132 by Dr. Charles Cantor have been thoroughly reviewed but were not found persuasive to overcome the rejection. The response dated 5/28/2007 asserts that the concept of linkage disequilibrium in genetics embodies the phenomenon that a disease-associated region in the human genome contains a cluster of polymorphisms associated with a disease state and asserts that identifying multiple polymorphisms associated with a disease state also identifies a region associated with the disease state consistent with the concept of linkage disequilibrium, and cites a portion from "Cantor & Smith, Genomics, 1999, page 192, which states "markers very close to the disease gene will tend, more likely than average, to retain the haplotype of the original chromosome because, as the distance to the disease shrinks, it becomes less likely that recombination events have occurred in this particular region". The response further asserts that the specification analyzed

several polymorphisms in the region of the human genome specified by claim 1 and 53 and identified several associated with breast cancer. The response asserts that 16 polymorphisms where identified that were associated with breast cancer with a p value of less than .05 of the 63 polymorphisms analyzed in the claimed region and thus have provided a written description for the claimed subject matter because Applicant identified a region associated with breast cancer by virtue of identifying several polymorphisms associated with breast cancer in the claimed region. These arguments have been thoroughly reviewed but were not found persuasive.

With regard to the assertion that 16 polymorphisms were found with a p value of less than 0.05, it is noted that in the presently claimed region, only 9 polymorphisms had a p value less than 0.05, out of 16 polymorphisms, that is about 50% (see table 19). Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from table 19, that a polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 2 is not predictably associated with breast cancer.

The declaration by Dr. Charles Cantor, at section 3, asserts that the patent application presents a genomic study in which many SNPs spaced throughout the entire genome were typed in two populations, a breast cancer population and a "healthy" control population., where regions that contained multiple disease associated polymorphisms were verified as being statistically associated with breast cancer, one region encoding the MAPK10 protein. The declaration asserts that several polymorphisms were typed in this region, several of which were found in a sub region or "hot zone", illustrated in figure 15. At section 4, the declaration reiterates arguments with regard to LD made in the response dated 5/28. These arguments have been thoroughly reviewed but were not found persuasive. The office action does not question the methodology

used by applicants to arrive at a region that warranted further study to determine breast cancer disease association. However, while these methods can identify a region that warrants further study, it does not provide a description of a representative number of specific alleles within the region which are disease associated vs not. This is exemplified by the data in table 19. Of 16 SNPs identified by applicants in the "hot zone", only 9 had a p value less than 0.05.

At section 5, the declaration provides citations of several references as a showing that "identifying a disease associated region by this methodology is supported by the work of other researchers". This argument has been thoroughly reviewed, however the claims are not drawn to methods of identifying disease associated regions, but rather to identifying a human subject at risk of breast cancer by detecting the presence of any specific polymorphic variation within the region. As already noted above, in the instant specification, only 9 of the 16 SNPs in the claimed subregion had a p value of less than 0.05. With regard to the references cited, while whole genome scanning methods were used to identify a CFH region associated with AMD, the references do not teach that based on this screen alone, the skilled artisan would be able to determine which polymorphic variants are disease associated. For example, there are currently 566 SNPs in the CFH gene region taught in NCBI, however, Hageman only discusses haplotypes with 8 SNPs.

At section 6, the declaration asserts that the inventors typed a significant number of polymorphisms in the MAPK10 region in the process of determining that the region was associated with breast cancer, and more specifically, 83% of the polymorphisms currently in the HapMap database having a minor allele frequency of greater than 0.5 in the claimed region. The declaration asserts that the inventors therefore have analyzed a significant number of

polymorphisms. This argument has been thoroughly reviewed but was not found persuasive as the SNPs analyzed provide no indication as to which of the additional polymorphic variants identified after the invention was filed, are disease associated vs not. The Board in Ex parte Kubin 83 USPQ2d 1410 (Bd. Pat. App. & Int 2007), citing *Eli Lilly*, 119, F.3d at 1568, 43 USPQ2d at 1406, held that, sufficient description to show possession of a genus "may be achieved by means of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." The specification provides no structure/function relationship nor any additional identifying characteristics which would allow the skilled artisan to determine which of the additional SNPs are within the genus of "breast cancer associated" SNPs. The Board additionally held that "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus", citing *University of Rochester*, 358 F. 3d at 927, 69 USPQ2d at 1895. Although the specification teaches how to test other SNPs for disease association, it has not described which of these specific variations are disease associated vs not, within the genus. Without a correlation between structure and function, the claim does little more than define the claimed inventions by function. Accordingly, the assertions made in the response dated 8/1/2007, page 2, last para to page 3, are not found persuasive. For these reasons and the reasons already made of record, the rejection is maintained.

8. Claims 1-2, 6, 19, 53-55, 75-76, and 84-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a human

subject at risk of breast cancer comprising a) detecting the presence of a C at nucleotide position 36424 of SEQ ID NO: 2 and b) identifying the human subject as having an increased risk of breast cancer or administering a breast cancer detection procedure, does not reasonably provide enablement for the methods as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying a human subject at risk of breast cancer comprising detecting the presence or absence of one or more polymorphic variations associated with breast cancer, in a region between about chromosome position 87330326 (position 23826 of SEQ ID NO: 12; rs2575674 and about chromosome position 87342924 (position 36424 of SEQ ID NO: 2; rs1541998) according to build 33 of Genbank, whereby the presence of the polymorphic variation is indicative of the subject being at risk of breast cancer, or administering

a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids, in a human subject and a risk for breast cancer.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 2 is a nucleotide sequence of a MAPK10 "region" (page 3). The specification teaches that a number of polymorphisms were identified in the sequence and teaches that a C variation at position 36424 of SEQ ID NO: 2 is statistically associated with breast cancer ($p=0.0070$; see page 78, table 6B). The specification teaches that a number of SNPs were identified in females with breast cancer (cases) and females without cancer (controls) and that SNPs were considered as being associated with breast cancer if the allele frequency between cases and controls was statistically significant (page 74, para 0247).

The specification teaches 68 SNPs in the "MAPK10 proximal region" were found (page 96, table 19), but only 17 have p values of less than 0.05. Regarding the claimed region, the specification teaches that of 16 polymorphisms found, 9 had a p value of less than 0.05 (see table 19). Although the declaration under 37 CFR 1.132 by Dr. Charles Cantor asserts this region is a "hot zone", it is clear from table 19, that a polymorphic variation, by virtue of being in the claimed region of SEQ ID NO: 2 is not predictably associated with breast cancer. The specification teaches no structure/function correlation between the members of the genus of specific polymorphisms in the claimed region that are associated with breast cancer risk.

The specification provides no universal correlation that any SNP in the claimed region would be associated with breast cancer nor does it provide any way to predict which sequences within the broadly claimed sequences would be "breast cancer associated". Of 16 disclosed polymorphic variations, the specification teaches a statistically significant association between only 9 positions and breast cancer.

It is clear from table 19, that a SNP, by virtue of being in the MAPK10 "region" or a region spanning that noted at page 4, is not necessarily associated with breast cancer. The specification provides no predictable correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for breast cancer risk or detection. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 36424 of SEQ ID NO: 2), but only teaches 2 out of 4 possible variations at each position (T/C at position 36424). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether these particular nucleotide variants even exist. Additionally, the specification provides no guidance as to how the SNP at 36424 (C), or any of the other 16 statistically significant variants, function to provide for increased risk of breast cancer. The specification provides no structure/function correlation between the disclosed SNPs and breast cancer for the skilled artisan to be able to predict which other positions within the claimed sequences might be predictably associated with the claimed phenotypes. It is not clear if any other variant at that position would have the same effect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at

issue, and the actual gene which is involved in the detected breast cancer association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of SEQ ID NO: 2, nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach the function or biological activity of mutations in MAPK10 with regard to breast cancer or therapeutic response. The specification demonstrates the unpredictability of this invention since 7 out of 16 of the identified SNPs in the claimed subregion of SEQ ID NO: 2 were not statistically significant and do not appear to be breast cancer associated given the data in the specification. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene

polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789).

Further, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph).

In the instant case, the specification only provides information that the T/C variant exists in humans and is associated with breast cancer, but provides no guidance that it has any effect whatsoever on the expression or activity of human MAPK10 or the broadly claimed sequences let alone any potential association with therapeutic effect.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of individual positions in the claimed region to determine whether any alteration at each position is associated with breast cancer and to identify which variations are predictably associated with breast cancer in any human subject. As neither the art nor the specification provide guidance as to which alterations at positions throughout the claimed region of MAPK10 are predictably associated with breast cancer, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the broadly claimed genomic sequences, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the

quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

9. Claims 1-2, 6, 9, 53-55, 75-76 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The nucleotide sequence surrounding and comprising the region between about chromosome position 87330326 and about chromosome position 87342924 according to Build 33 of the GenBank database human genome sequence is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

The claims to "region between about chromosome position 87330326 and about chromosome position 87342924 according to Build 33 of the GenBank database human genome sequence" to give contextual reference for polymorphisms disclosed in the specification and in the claims.

MPEP 608.01 (p)[R-2] teaches that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The recitation of a Build 33 of the GenBank database constitutes an attempt to incorporate by reference the subject matter which is contained within the recited GenBank database record. This recitation constitutes an improper incorporation by reference of essential material since it is material that is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (MPEP 608.01)(p).

Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention.

Response to Arguments

10. The response dated 5/28/2007 and 8/1/2007 traverses the enablement rejection. The response asserts that the specification identifies a region specified in claims 1 and 53 as associated with occurrence of breast cancer and assert that applicants finding paves the way toward identifying and using polymorphisms of this region and asserts that the finding that the region specified in claim 1 and 53 guides the person of ordinary skill in the art toward routinely identifying any other polymorphisms associated with breast cancer in that region. This argument has been thoroughly reviewed but not found persuasive. Associating polymorphisms with a disease is not routine experimentation and as taught by Kroese, a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Furthermore, Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests. Therefore, associating any other polymorphism within the claimed genome is replete with unpredictable experimentation and is considered undue and not routine.

The response asserts, that the specification provides multiple working examples in support of the claimed subject matter and routine experimentation does not preclude a finding of

enablement. The response asserts that the methodology for identifying polymorphisms associated with breast cancer in DNA from a human subject and methods for isolating DNA from human blood samples. The response further asserts that a person of ordinary skill in the art could apply these methods in a routine matter to polymorphisms in the claimed region. This argument has been thoroughly reviewed but not found persuasive. The working examples in the specification demonstrate the unpredictable nature of the claimed invention as 7 out of 16 SNPs in the claimed region were not statistically associated (see table 19). Of 16 SNPs identified by applicants in the termed "hot zone", only 9 had a p value less than 0.05. The response dated 8/1/2007 adds that the declaration under 37 CFR 1.132 by Dr. Charles Cantor sets forth that applicants analyzed 83% of the polymorphisms currently in the HAPMAP database with a minor allele frequency greater than 0.05 in the claimed subregion. However, it is noted that as set forth above, almost half y of the polymorphisms analyzed in the claimed subregion, for which data is provided in the specification, were NOT found to be associated. The specification provides no predictable correlation as to which polymorphisms in the claimed subregion are disease associated vs not. As previously noted, merely identifying a polymorphism in the claimed subregion, is in most cases, not predictive of disease. The field of associating polymorphisms with disease states is highly heterogeneous, as acknowledged by the art. Further, even if one study finds an association, it is not necessarily predictive that such an association actually exists, as further studies have been found to refute the earlier analysis, in many cases. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance

provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The response asserts that the CAFC found enablement in *In re Wands* are applicable to the same finding of enablement here. The response asserts that the technology in Wands is similar to the technology described in the present specification in the sense that the person of ordinary skill in the art is prepared to screen additional polymorphisms in the region specified by claim 1 and 53. The response asserts that the rational in *In re Wands* is applicable to the finding of enablement here. This argument has been thoroughly reviewed but not found persuasive. The claims are not drawn to a screening assay. The claims are drawn to a method of identifying a subject at risk of breast cancer and the claims require the knowledge that a specific polymorphism is associated with breast cancer. The claims do not recite a method of screening polymorphisms to determine *if* the polymorphism is associated with breast cancer. The claimed invention is not applicable to the rationale in *In re Wands* as the claimed invention is not a screening assay. The response asserts that the high level of skill in the art leads to the conclusion that any experimentation associated with the full claim scope is routine and not undue. Accordingly the specification provides an enabling disclosure of the claimed subject matter. However, as stated, associating any polymorphisms within the claimed region of the human genome is unpredictable experimentation and is undue. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

11. Claims 1, 2. 6, 19, 53-55, 75-76 and 84-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 53, 75 and 84 recites the phrase "about chromosome position 87330326 and about chromosome position 87342924 ... according to build 33 of the GenBank database human genome sequence" to indicate a region from MAPk10, however neither the claims nor the specification provide an indication as to what the metes and bounds of "about chromosome position 87330326 " or "about chromosome position 87342924". First, the chromosome these positions correspond to is not recited in the claim. Second, neither the specification nor the claims provide guidance as to how far outside the indicated positions would still be considered to be at "about" the indicated positions. Accordingly, the metes and bounds of the region encompassed by the claimed recitation is unclear.

Claims 1, 53, 75, and 84 are indefinite in the recitation of "presence or a absence of a polymorphic variation... in a region between about chromosome position 87330326 and about chromosome position 87342924 ... according to build 33 of the GenBank database human genome sequence" because is not clear what the actual polymorphic variation is, in other words, for position 87342924, for example, is the variant the T or C at that position? The specification teaches that either allele exists but does not define what the "variant" is. However, one would not be able to identify a subject as being at risk of breast cancer simply by detecting that the position is polymorphic. but rather by detecting the presence of the disease associated allele. However, the claim does not make clear what that allele is.

Claim Rejections - 35 USC § 102

12. Claims 1, 6 75 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by dbSNP rs1541998 (publicly available in build 88, 2000).

rs1541998 teaches the detection of polymorphic alleles C/T in homo sapiens. Although the claims are directed to identifying a subject at risk of breast cancer, it is noted that the claims are directed to detecting the presence or "absence" of a polymorphic variation, which is interpreted as encompassing detecting the C allele. There is no active step relating back to the preamble relating to the "absence" of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the "absence" of the variation.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 2, 6, 19, 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over rs1541998 in view of Soderlund (Soderlund et al; US Patent 6,013,431).

rs1541998 teaches the detection of polymorphic alleles C/T in homo sapiens. Although the claims are directed to identifying a subject at risk of breast cancer, it is noted that the claims are directed to detecting the presence or "absence" of a polymorphic variation, which is interpreted as encompassing detecting the C allele. There is no active step relating back to the preamble relating to the "absence" of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the "absence" of the variation.

rs1541998 does not specifically teach any particular method of detection, obtaining a nucleic acid sample from the subject, or hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products, however Soderlund teaches methods of detecting specific nucleotide variations in the nucleic acid sample of a subject by hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products (see abstract, figures 1-3, col. 8). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine the identity of the polymorphism at

rs1541998 using the methods of Soderlund because Soderlund teaches that such methods are suitable for identifying the allele of a polymorphic position

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays. NOTE: the examiner will be on maternity leave for a portion of December 2007 as well as the months of January and February 2008.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634

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/Jehanne Sitton/
Primary Examiner
Art Unit 1634
11/29/2007